PATENT APPLICATION

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June 13, 2002
Date

Jennifer K. Johnson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Conklin, Darrell C. et al.
Application No.	:	09/186,642
Filed	:	November 4, 1998
For	:	A HUMAN 2-19 PROTEIN HOMOLOGUE, Z219C

Examiner	:	Eliane Lazar-Wesley, Ph.D.
Art Unit	:	1642
Docket No.	:	97-64
Date	:	June 13, 2002

Commissioner for Patents
Washington, D.C. 20231

Declaration of Theodore E. Whitmore Under 37 CFR § 1.132

Sir:

I, Theodore E. Whitmore, Ph.D., hereby declare as follows:

1. I am Senior Scientist, Genetics, at ZymoGenetics, Inc.; the assignee of the above-identified application.

2. I have reviewed and understand the specification and claims of the above-identified application. More specifically, I have read and understood page 71, line 33, to page 74

line, 7; page 72 lines 12-30, and Example 3 (page 87) of the specification that pertain to the use of z219c polynucleotides as a marker for chromosomal abnormalities and human cancers.

3. In addition, I have read and understood the following references: Shridhar, V. et al, Oncogene, 12:1931-1939, 1996 (copy of record); Shridhar, R. et al, Cancer Res., 56:5576-5578, 1996 (copy of record); Ohta, M. et al, Cell 84: 587-597, 1996 (copy enclosed); Wang, N. et al., Cancer Genet. Cytogenet. 11: 479-481, 1984 (copy enclosed); and Sozzi, G. et al., Cell 85: 17-26, 1996 (copy enclosed).

4. I have performed additional experiments concerning the chromosomal localization of the z219c gene as described below.

5. The chromosomal mapping position shown in Example 3 of the specification (p. 87) shows that z219c maps to the 3p21.1-p13 region of chromosome 3. I have performed experiments that further define a more precise locus for z219c within the 3p21.1-p13 region. The z219c locus is further refined to the 3p14.2 locus by use of an alternative distal framework marker SGC33932 that is mapped equal distance from D3S1313 on the Whitehead Institute/MIT Center for Genome Research's radiation hybrid map of the human genome. Now, both the proximal and distal framework markers can be found on the NCBI gene map of the human genome (National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD) (http://www.ncbi.nlm.nih.gov/genemap99/). Both markers are positioned in the 88.2 cM / 198.02 cR_3000 (1 cR_3000 = ~270 kb) interval on the NCBI GeneBridge 4 (GB4) version of Chromosome 3.

It is well recognized that gross chromosomal aberrations such as deletions, LOH, and translocations in the 3p21.1-p13 region of chromosome 3 are associated with human cancers. In addition, it is well established that gross chromosomal aberrations such as deletions, LOH, and translocations in the 3p14.2 locus, wherein the z219c gene is located is associated with human cancers. For example, the fragile histidine triad gene, FHIT, which maps to 3p14.2 (Ohta, M. et al, Cell 84: 587-597, 1996, copy enclosed), is also positioned in the same interval and between the same proximal and distal markers as z219c. This indicates that z219c is in close proximity to FHIT gene (±270 kb) and the most common of the constitutive aphidicolin-inducible fragile sites, FRA3B, of which the FHIT gene is a part (Ohta, M et al., supra.). The FRA3B fragile site

locus is included in an approximate 200 to 300 kb specific region of chromosome 3p14.2 that is homozygously deleted in multiple tumor-derived cells lines and associated with renal cell carcinoma (Ohta, M et al., supra. ; and Wang, N. et al., Cancer Genet. Cytogenet. 11: 479-481, 1984, copy enclosed). Aberrant transcripts of the FHIT locus have also been found in approximately 50% of esophageal, stomach, and colon carcinomas (Ohta, M et al., supra.) as well as lung cancers of the small cell (SCLC) and nonsmall cell (NSCLC) type (Sozzi, G. et al., Cell 85: 17-26, 1996, copy enclosed). The presence of diseases associated with gross chromosomal aberrations such as translocations and rearrangements within 3p14.2, the refined locus of z219c gene, further support the initial observations that z219c polynucleotide probes can serve as a diagnostic for gross chromosomal aberrations such as deletions, LOH, and translocations and rearrangements as described in the patent application.

The patent application discusses the use of z219c polynucleotide probes to detect chromosomal abnormalities on Chromosome 3 (page 71, line 33, to page 74 line, 7; page 72 lines 12-30). More specifically, it is recognized in the art that the region in which z219c is localized, 3p21.1-p13 region, and more specifically, the 3p14.2 locus is a common hot spot for translocation (i.e., gross chromosomal rearrangement) and large deletions (e.g., described above) seen in human cancers, particularly renal cell carcinomas, including nonpapillary, papillary and oncocytomas (Shridhar, V. et al, Oncogene, 12:1931-1939, 1996, cited in the specification, show that chromosome 3p breakage, translocation and LOH at 3p14 is common in renal cell carcinomas, including nonpapillary, papillary and oncocytomas): and hereditary renal cell carcinoma (3p14 translocation breakpoint and loss, Shridhar, R. et al, Cancer Res., 56:5576-5578, 1996 cited in specification (Copy of record). The additional experimentation I have performed further narrows the locus for 219c, demonstrating that it is not unreasonable that one could use z219c polynucleotide probes as a diagnostic, to detect chromosomal abnormalities on Chromosome 3 to detect such common gross chromosomal abnormalities in and around the 3p14.2 locus, such as chromosomal translocations or rearrangements commonly seen in these human cancers.

6. The 3q21.1-p13 locus, and more specifically the 3p14.2 locus, would be immediately appreciated by one of skill in the art as a critical region for translocations involved

in human malignancies and tumors. Such information is disclosed in the application at page 71, line 33, to page 74 line, 7; page 72 lines 12-30, and it would be readily apparent to one reading this application that the z219c polynucleotides disclosed in the application could be used in for such purposes. As a person who recognizes the usefulness and need of additional chromosomal markers in diagnosing human disease, I recognize that the utility of new markers in this region of chromosome 3, such as the z219c polynucleotides disclosed in the application. Using z219c polynucleotides as a chromosomal and cancer diagnostic is not unreasonable, and is in fact desirable, as multiple polynucleotide markers within a region add to the specificity and information surrounding the chromosomal aberration in question and cancer diagnosis.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that the making of willfully false statements and the like is punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and may jeopardize the validity of any patent issuing from this patent application.

By Theodore E. Whitmore Date 06/13/02

Theodore E. Whitmore